REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of this application in light of the amendments and arguments presented herein. Applicants have submitted herewith a Request for Continued Examination.

The Applicants thank Examiner Sheikh for the courtesy he extended to Applicants' representative Michelle Glasky Bergman during a telephonic interview on March 29, 2010.

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 are pending in this application.

Claim 1 has been amended to recite the process by which the microparticles are formed. Support for this amendment can be found in the published specification in paragraph [0061]. Claims 1, 7 and 14 have been amended to recite that the "particles are maximally retained in the nasal cavity." Support for maximal retention of the microparticles in the nasal cavity can be found in paragraph [0013].

Claims 7 and 14 have been amended to comport with the amendments to claim 1. Claims 20 and 21 have been amended to clarify the term "microparticles."

New claims 22 and 23 further limit claims 1 and 7. Support for new claims 22 and 23 can be found in the published application in paragraph [0061].

No new matter has been introduced as a result of the claim amendments.

35 U.S.C. §112 Rejections

Claim 1 has been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office asserts that the term "preferentially"

renders the claim indefinite. Claim 1 has been amended to remove the term "preferentially." Therefore, Applicants respectfully request withdrawal of the rejection on this basis.

35 U.S.C. §103 Rejections

Claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 have been rejected under 35 USC §103(a) as allegedly being unpatentable over Steiner et al. (US Pat. 5,503,852) in view of Illum (US Pat. 5,690,954). Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

The instant claims are drawn to compositions, devices and methods for nasal administration of antihistamines in a dry powder the dry powder form made by a process comprising the steps of providing diketopiperazine microparticles between 10

and 20 microns in diameter; suspending the diketopiperazine microparticles in an aqueous medium with an antihistamine to form a suspension; and forming antihistamine-coated diketopiperazine microparticles by removing solvent from the suspension; wherein the antihistamine-coated diketopiperazine microparticles are between about 10 microns and about 20 microns in diameter and more than 50% of the microparticles have a particle size greater than about 10 microns, and wherein the particles are maximally retained in the nasal cavity and the composition does not pass into the pulmonary system.

Steiner discloses particles between 0.1 to 10 microns in diameter. Steiner does not disclose microparticles wherein more than 50% of the microparticles have a particle size greater than about 10 microns. The microparticles of Steiner are primarily used for delivery to the pulmonary system, a use requiring smaller particles. Furthermore, the particles of Steiner are formed by co-precipitation of the diketopiperazine and the drug from a solution to form microparticles, rather than coating of the drug (antihistamine) on the surface of a preformed diketopiperazine microparticle. Therefore, Steiner does not teach or suggest drug-coated microparticles wherein the majority of the particles are greater that 10 microns in size and furthermore, Steiner does not suggest particles which are retained maximally in the nasal cavity, rather than passing into the lungs.

The microparticles of Steiner are prepared by a process of co-precipitation in which the diketopiperazine is dissolved in a solution and then the solution is mixed with a second solution containing the active agent. The microparticles are then precipitated by the addition of acid or base (Steiner column 9, line 55 through column 10, line 8). The resultant microparticles have the active agent encapsulated within the diketopiperazine microparticle during the co-precipitation process.

In contrast, the microparticles of the instant invention are formed by obtaining pre-formed microparticles of diketopiperazine of a controlled size (10-20 microns) and mixing the pre-formed microparticles with an antihistamine such that the antihistamine is coated on the surface of the diketopiperazine microparticles (see Example 5 of the instant specification). As asserted by Dr. Marshall Grant in the Declaration under 37 CFR §1.132 submitted on August 10, 2009 in the instant application, the coated

microparticles of the instant claims (termed "complexed" by Dr. Grant) and the co-precipitated microparticles of Steiner have different physical and physicochemical characteristics (see Grant declaration, paragraphs 11-18).

Furthermore, the Applicants own publication (Wilson et al. Respiratory Drug Delivery VIII, 2002), submitted as Exhibit B of the Grant Declaration and published after the priority date of the instant application, states that particles prepared for inhalation have typical physical and aerodynamic characteristics that direct them to the deep lung. Particles for delivery to the deep lung have mass mean aerodynamic diameter of 2-4 microns. The authors go on to state that the goal of the published study (the subject of the instant application) was to produce larger particles for nasal inhalation (at least 10 microns in diameter) to reduce drug carry-over to the taste centers and more precisely target the nasal mucosa (maximally retain the microparticles). (See Wilson page 545, Introduction). Therefore, the Wilson reference establishes the 10 micron critical lower limit of drug-coated diketopiperazine microparticle size for optimal nasal administration without deposition of the microparticles in the taste centers or in the deep lung.

Illum does not remedy the deficiencies of Steiner. Illum teaches drug delivery systems comprising microsphere particles containing an active drug and a bioavailability enhancer. Illum does disclose antihistamines as part of a long list of drugs (column 8, line 59 through column 9, line 52). Illum states that the microspheres should be of a size between 10 and 100 microns (column 6, lines 13-14). In column 6, line 28 through column 7, line 54, Illum presents examples of microspheres and their sizes. Starch microspheres were prepared having a mean size of 33 microns (column 6, lines 52-53); albumin microspheres were prepared having a size range of 40-60 microns (column 7, lines 1-2) and a mean size of 43 ± 6 microns (column 7, lines 19-20); gelatin microspheres were prepared having a mean particle size of 70 microns (column 7, lines 30-31) and 60 microns (column 7, lines 41-42); and chitosan microspheres were prepared having a size range of 10-90 microns (column 7, lines 53-54). While Illum teaches microspheres made from a variety of materials, none of the materials produced microparticles in which the majority of the microparticles are in the range of 10-20 microns. In fact, the majority of the microspheres produced by Illum are greater than 20

microns in size, teaching away from the instant claims which recite microparticles of 10-20 micron size as optimal for effective delivery of drugs to the nasal mucosa.

While there is overlap in the range of the claimed microparticles and the microspheres of Illum, Illum does not teach or suggest drug coated diketopiperazine microparticles between about 10 microns and about 20 microns in diameter wherein more than 50% of the microparticles have a particle size greater than about 10 microns.

Accordingly, the teaching of Steiner in combination with Illum fails to teach or suggest all elements of the claimed invention and there is no suggestion to combine the references. Therefore the Office has not established *prima facie* obviousness of claims 1, 3-5, 7, 8, 10-12, 14, 16-18, 20 and 21 over Steiner in view of Illum. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the foregoing, Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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